A Slit/miR-218/Robo regulatory loop is required during heart tube formation in zebrafish.

Journal: Development

Publication Year: 2011

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PubMed link: 21385766

Funding Grants: microRNA Regulation of Cardiomyocyte Differentiation from Human Embryonic Stem Cells, The Gladstone CIRM Shared Human Embryonic Stem Cell Core Laboratory

Public Summary:
Members of the Slit family of genes encode a corresponding set of secreted proteins that interact with receptors called Robo to provide guidance cues for many cell types. For example, Slit/Robo signaling elicits repulsion of nerve cells called axons during neural development, whereas in the cells that line the interior surface of blood vessels, called endothelial cells, this pathway inhibits or promotes the growth of new blood vessels, depending on the cellular context. MicroRNAs are short strands of RNA that regulate gene expression. Here, we show that a microRNA called miR-218 is embedded in the slit2 and slit3 genes and that it suppresses Robo1 and Robo2 expression. Our data indicate that miR-218 and multiple Slit/Robo signaling components are required for heart tube formation in zebrafish. This signaling network modulates the previously unappreciated function of vascular endothelial growth factor (VEGF) signaling in this process. VEGF is a signaling protein that stimulates the growth of new endothelial cells and blood vessels.These findings suggest a new paradigm for the ways in which microRNAs can control the interactions between molecules and proteins on or within a target cell and provide evidence for a novel signaling pathway regulating vertebrate heart tube assembly.

Scientific Abstract:
Members of the Slit family of secreted ligands interact with Roundabout (Robo) receptors to provide guidance cues for many cell types. For example, Slit/Robo signaling elicits repulsion of axons during neural development, whereas in endothelial cells this pathway inhibits or promotes angiogenesis depending on the cellular context. Here, we show that miR-218 is intronically encoded in slit2 and slit3 and that it suppresses Robo1 and Robo2 expression. Our data indicate that miR-218 and multiple Slit/Robo signaling components are required for heart tube formation in zebrafish and that this network modulates the previously unappreciated function of Vegf signaling in this process. These findings suggest a new paradigm for microRNA-based control of ligand-receptor interactions and provide evidence for a novel signaling pathway regulating vertebrate heart tube assembly.